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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/058,323	04/09/1998	BEREND HOUWEN	10690/101683	7347

7590 07/22/2002
BRYAN CAVE
245 PARK AVENUE
NEW YORK, NY 101670034

EXAMINER

GABEL, GAILENE

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 07/22/2002

26

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

09/058,323

Applicant(s)

HOUWEN ET AL.

Examiner

Gailene R. Gabel

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 June 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 2 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☐ they raise the issue of new matter (see Note below);
 - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

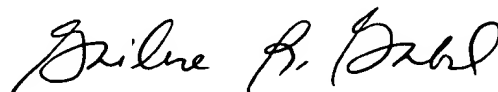
NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: NONE.Claim(s) objected to: NONE.Claim(s) rejected: 1-11.Claim(s) withdrawn from consideration: NONE.

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☐ Other: _____



Continuation of 5. does NOT place the application in condition for allowance because: applicant's argument is not persuasive. Additionally, the claims as recited, fail to obviate the prior art of record.

DETAILED ACTION

Applicant's Response

1. Applicant's response filed 6/13/02 in Paper No. 26 is acknowledged. Currently, claims 1-13 are pending and under examination.

Rejections Maintained

Claim Rejections - 35 USC § 102103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1-3 and 5-9 stand rejected under 35 U.S.C. 102(e) as being clearly anticipated by Kim et al. (US 5,648,225) for reason of record.

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3. Claims 4 and 10-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (US 5,648,225) in view of Inami et al. (US 5,298,426) for reason of record.

Response to Arguments

4. Applicant's arguments filed 1/24/02 have been fully considered but they are not persuasive.

A) Applicant argues that Kim does not describe or suggest "a mixture of the nuclear stain and the monoclonal antibodies in one analytical reagent".

In response, the claimed method does not appear to define such feature: "a mixture of the nuclear stain and the monoclonal antibodies in one analytical reagent".

B) Applicant argues that Kim does not describe or suggest "a mixture of the nuclear stain and the monoclonal antibodies in one method" and does not suggest that the nuclear stain and monoclonal antibodies can exist together.

Contrary to Applicant's argument, Kim discloses that the multipurpose reagent system includes salts and buffers, as well as nuclear stain and antibody against cell surface antigens for use in rapid analysis of a whole blood sample, allowing determination of at least five classes of peripheral white blood cells and nucleated red blood cells (see Abstract and column 6). Further, Kim does, teaches the method as claimed by Applicant. Specifically, Kim teaches how the multipurpose reagent system is used in a method of discriminating and counting between leucocytes and erythroblasts

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or nRBCs. Kim teaches adding 1) fluorochrome-conjugated antibodies directed to leucocyte surface antigens, 2) nucleotide fluorescent dye, i.e. ethidium homodimer, and 3) a proper concentration of aldehydes, salts, and buffer, in a multipurpose reagent system, to an anticoagulated blood sample, incubating the mixture, and subjecting the mixture to flow cytometric analysis. The fluorochrome-conjugated antibodies directed to leucocyte surface antigens bind and stain leucocytes. The nucleotide fluorescent dye stains the exposed nuclei of erythroblasts, but does not penetrate the intact white cells, thus allowing quantitative analysis of nucleated red cells. The mixture of aldehydes, non-quaternary mono-ammonium salt, and buffer permeabilizes, i.e. lyses, the erythroblasts while maintaining the integrity of the fixed white blood cells. Electronic signals from scattered light collected from different angles and fluorescence intensities are plotted as two- dimensional plots in column 6, lines 31-46 and also Figure 3. Given that Kim et al. teaches all the limitations recited in the rejected claims, it is maintained that claims 1-3 and 5-9 are anticipated by Kim. As recited, no patentable distinction is seen between the .

C) Applicant argues that the combination of the teaching of Kim and Inami does not suggest the affirmative and manipulative steps taken with respect to the two signals appearing in Applicant's claims such as detecting, analyzing, and discriminating. Applicant also argues that there is no suggestion and motivation to combine the teaching of Kim and Inami and that Examiner's explanation of the motivation supporting the combination underlying the rejection is insufficient.

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In response, the affirmative and manipulative steps taken with respect to the two different signals incorporating the detection, analysis, and discrimination of two distinct populations by virtue of a nuclear stain at a specific wavelength for one population, and fluorescent labeled cell surface antigen (via monoclonal antibody conjugation) at a specific wavelength for the other population, are a function of flow cytometric analysis and both of Kim and Inami incorporate use of such system to “differentiate” and “classify” populations of cells in their methods. As such, these “manipulative steps” are accounted for, for flow cytometric analysis to work. The simultaneous detection, analysis, and discrimination between populations of cells having distinct stains and labels, manipulation of results obtained, and evaluation of population distribution in a histogram, are precisely the power of flow cytometric analysis.

To reiterate, Kim teaches combining 1) fluorochrome-conjugated antibodies directed to leucocyte surface antigens, 2) nucleotide fluorescent dye, and 3) a proper concentration of aldehydes, salts, and buffer, in a multipurpose reagent system, in order to simultaneously quantitate and discriminate between leucocytes and nucleated RBCs using fluorescent signal analysis by flow cytometry. Inami is incorporated for the “two-reagent system” to substitute for the buffer solution taught by Kim so that the erythroblasts are not lysed, but rather, their cell membranes are increased for permeability of a nucleotide fluorescent dye while the integrity of the cell membrane of leucocyte population is maintained; Inami, likewise, uses fluorescent signal analysis by flow cytometry to differentiate erythroblasts from other leucocytes.

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It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the buffer solution of Kim with the two reagent system taught by Inami for use in permeabilizing erythroblasts because Kim specifically taught that integrity and antigenicity of white blood cells need to be optimally maintained during permeabilization, i.e. lysing, of the nRBC's or erythroblasts in order to allow accurate simultaneous quantitation of both populations and Inami specifically taught that the two reagent system eliminates lysing conditions for erythroblasts while maintaining the integrity and shape of WBCs for accurate differentiation of both erythroblast and leucocyte populations.

5. For reasons aforementioned, no claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
July 16, 2002



CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/641